Ombitasvir, Paritaprevir/Ritonavir and Dasabuvir (Viekira Pak™) and Ombitasvir, Paritaprevir/Ritonavir (Technivie™)

Criteria for Use

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives and Office of Public Health

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.** *The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.*

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive this regimen without local adjudication.*

☐ Limited Life Expectancy (refer to issues for consideration)

☐ Documented ongoing nonadherence to prescribed medications or medical treatment, failure to complete hepatitis C virus (HCV) disease evaluation appointments and procedures or unable to commit to scheduled follow-up/monitoring for the duration of treatment

☐ Known hypersensitivity to ombitasvir, paritaprevir, ritonavir, or dasabuvir (if applicable) or any other component of this direct acting antiviral based-regimen

☐ HIV/HCV co-infection in patients not receiving antiretroviral therapy OR where antiretroviral drug-interactions preclude the use of Viekira or Technivie (Refer to Issues for Consideration and http://www.hep-druginteractions.org for a list of acceptable drugs)

☐ Decompensated liver disease (i.e., Child-Pugh score ≥7 (i.e. Class B or C), MELD score ≥15, and/or clinical manifestations)

☐ Previous virologic failure to regimens containing an NS3-4A protease-inhibitor, NS5B-inhibitor or NS5A inhibitor

☐ HCV **genotype 2, 3, 5 or 6** infection

☐ **HCV genotype 4 with cirrhosis and/or history solid organ transplant** (refer to Issues for Consideration and ledipasvir/sofosbuvir CFU)

☐ Patient receiving ethinyl estradiol containing product(s)

Drug interactions

☐ For Viekira, co-administration with 1) drugs that are highly dependent on CYP3A for clearance such as lovastatin and simvastatin and for which elevated plasma concentrations are associated with serious and/or life-threatening events; 2) drugs that are strong inducers of CYP3A and CYP2C8 such as rifampin or St. John's wort and may lead to reduced efficacy of Viekira; OR 3) drugs such as gemfibrozil that are strong inhibitors of CYP2C8 and may increase dasabuvir plasma concentrations and the risk of QT prolongation

☐ For Technivie, co-administration with 1) drugs that are highly dependent on CYP3A for clearance such as lovastatin and simvastatin and for which elevated plasma concentrations are associated with serious and/or life-threatening events; 2) drugs that are strong inducers of CYP3A such as rifampin or St. John's wort and may lead to reduced efficacy of Technivie.

When Viekira or Technivie is used in combination with ribavirin:

☐ Contraindication and/or intolerance to ribavirin

- Contraindication is defined as history of significant or unstable cardiac disease, known pregnancy, positive pregnancy test, and men whose female partner is pregnant or plan to become pregnant, known hypersensitivity reaction, and/or significant anemia (i.e. symptomatic or baseline hemoglobin <10g/dL) and/or history of *significant* adverse events with previous ribavirin-containing regimen. **Please note that history of anemia related to ribavirin-containing regimen should be evaluated in context of PBM CFU for ESA (i.e., ribavirin dose reduction to 600mg must have been instituted prior to consideration of ESA use) and does not necessarily constitute intolerance.

Inclusion Criteria *The answers to all of the following must be fulfilled in order to meet criteria.*

☐ Treatment regimen and duration according to the dosage and administration section below

☐ Under care of and/or in collaboration with an experienced VA HCV practitioner

☐ Adherence counseling performed including laboratory follow-up and documented understanding by patient

☐ **Hepatitis C Virus Genotype 1 infection for Viekira or Genotype 4 without cirrhosis for Technivie**

For women of childbearing potential receiving ribavirin or who have a male partner receiving ribavirin

☐ When Viekira or Technivie regimen is used in combination with ribavirin therapy (which is pregnancy category X), it should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Two effective methods of contraception should be used during treatment with Viekira or Technivie and concomitant ribavirin, and for 6 months after treatment has concluded. Note: the co-administration of ethinyl estradiol-containing medications are contraindicated due to potential increase in liver function tests and must be discontinued prior to starting of Viekira or Technivie therapy. Alternative methods of contraception (e.g., progestin-only contraception or non-hormonal methods) are recommended. Routine monthly pregnancy tests must be performed during HCV therapy.

Dosage, Administration

Viekira for Genotype 1: Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg co-formulated tablets once daily (in the morning) **and** one dasabuvir 250 mg tablet twice daily (morning and evening) with a meal without regard to fat or calorie content. For certain patient populations, co-administration with ribavirin (in 2 divided doses) with food (<75 kg: 1000 mg/day or ≥75 kg: 1200 mg/day) is recommended. **Treatment regimen and duration are based upon patient characteristics as described in the Table 1 below.**

NOTE: Viekira Pak consists of ombitasvir, paritaprevir, ritonavir fixed dose combination tablets copackaged with dasabuvir tablets. Each weekly carton contains seven daily dose packs. Each daily dose pack contains four tablets: two 12.5/75/50 mg ombitasvir, paritaprevir, ritonavir tablets and two 250 mg dasabuvir tablets, and indicates which tablets need to be taken in the morning and evening.

Table 1. Viekira Treatment Regimen and Duration for HCV Genotype 1 based upon patient characteristics

Population includes patients with HCV monoinfected, HCV/HIV-1 co-infected stabilized on certain antiretroviral regimens or hepatocellular carcinoma (HCC)[a,b,c]	Dosage Regimens	Total Treatment Duration
Genotype 1a without cirrhosis	Viekira Pak plus ribavirin	12 weeks
Genotype 1a with compensated cirrhosis	Viekira Pak plus ribavirin	24 weeks[d]
Genotype 1b without cirrhosis	Viekira Pak	12 weeks
Genotype 1b with compensated cirrhosis	Viekira Pak with or without ribavirin[e]	12 weeks

[a]**Refer to Issues for consideration for alternative treatment options including pre- and post -transplant patients**
[b]Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.
[c]Population includes treatment-naïve and treatment-experienced patients with peginterferon/ribavirin.
[d]Viekira Pak plus ribavirin for 12 weeks may be considered for patients who are treatment naïve OR in patients with prior relapse or partial response to previous peginterferon/ribavirin treatment; Refer to Issues for Consideration for more detail.
[e]Prescribing information currently recommends Viekira Pak plus ribavirin; more recent trial data (i.e, Turquoise-III) evaluated Viekira without ribavirin in Genotype 1b patients with cirrhosis (100% SVR12 achieved in 60/60 patients).

Technivie for Genotype 4: Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg co-formulated tablets once daily (in the morning) with a meal without regard to fat or calorie content. Co-administration with ribavirin (in 2 divided doses) with food (<75 kg: 1000 mg/day or ≥75 kg: 1200 mg/day) is recommended.

Table 2. Technivie Treatment Regimen and Duration for HCV Genotype 4 based upon patient characteristics

Population includes patients with HCV monoinfected, HCV/HIV-1 co-infected stabilized on certain antiretroviral regimens	Dosage Regimens	Total Treatment Duration
Genotype 4 without cirrhosis[a]	Technivie plus ribavirin[b]	12 weeks

[a]Population: treatment-naïve and treatment-experienced patients with peginterferon/ribavirin.
[b]Technivie administered without ribavirin for 12 weeks may be considered for treatment-naïve patients who cannot tolerate ribavirin

Recommended Monitoring

In addition to standard clinical and laboratory monitoring in a patient receiving HCV therapy, the following monitoring is recommended for Viekira and Technivie regimen:

- **Baseline and on-going evaluation for potential drug-drug interactions:** Patient should be assessed for potential drug-interactions including over the counter products.
- **Hematologic adverse events (anemia) if co-administered with ribavirin:** Complete blood count with white blood cell differential counts should be obtained at baseline and at treatment weeks 2, 4, 8, and 12, and at other time points, as clinically appropriate. Initial management of anemia should consist of ribavirin dose reduction to 600mg for hemoglobin <10g/dL or sooner if clinically indicated; for additional monitoring and management of Hepatitis C treatment-related anemia refer to the PBM CFU for Recombinant Erythropoietin.
- **For patients with cirrhosis (i.e. Viekira only to be used in Child-Pugh A cirrhosis; Technivie not FDA approved for use in cirrhotics):** Monitor for clinical signs and symptoms of hepatic decompensation (such as ascites, hepatic encephalopathy, variceal hemorrhage). Hepatic laboratory testing including direct bilirubin levels should be performed at baseline and during the first 4 weeks of starting treatment and as clinically indicated. Discontinue in patients who develop signs or symptoms of hepatic decompensation.
- **ALT Elevations:** Monitor liver chemistry tests before initiating and during therapy.
- **Careful virologic monitoring** should be assessed to avoid the emergence of resistance. Patients should have HCV RNA assessed at week 4 of treatment; if the HCV RNA is detectable at week 4 or at any time point thereafter, HCV RNA should be reassessed in 2 weeks. If the repeated HCV RNA level has increased (i.e., >1 $\log_{10}$ IU/mL from nadir), discontinuation of all therapy should be strongly considered.
- **Sustained Viral Response (SVR) or relapse** should be determined by measurement of HCV RNA at the end of therapy and 12 weeks thereafter.
- **Ongoing assessment of treatment adherence** including medical appointments, laboratory follow-up and medications should be performed.
- **Monthly pregnancy tests** for women of childbearing potential receiving ribavirin

Issues for Consideration

Treatment Considerations

- **Viekira for Genotype 1: In genotype 1a patients with compensated cirrhosis, SVR rates varied by prior treatment history.** In genotype 1a naïve patients with cirrhosis, SVR rates were 92% (59/64) with 12 weeks and 95% (53/56) with 24 weeks of therapy. In prior relapsers treated with Viekira, SVR rates were 93% (14/15) in those treated for 12 weeks and 100% (13/13) in those treated for 24 weeks. In prior partial responders, SVR rates were 100% in patients treated for either 12 weeks (11/11) or 24 weeks (10/10). In prior null responders, SVR rates were 80% (40/50) for those treated for 12 weeks and 93% (39/42) for those treated for 24

weeks. **Based on these data, 12 weeks of treatment with Viekira may be considered in genotype 1a cirrhotic patients who are naïve or in whom prior relapse or partial response to previous peginterferon/ribavirin treatment has been documented and confirmed. Consider extending to 24 weeks for slow on-treatment virologic response on a case-by-case basis.**

- **Genotype 1 patients who had previous virological failure with a NS3-4A protease inhibitor or sofosbuvir-based regimen:** Viekira regimen has not been studied and therefore, cannot be recommended.
- **Genotype 4 patients with compensated cirrhosis:** Technivie plus ribavirin was only FDA approved for use in HCV genotype 4 patients without cirrhosis (as the pivotal phase 2b trial only enrolled patients without cirrhosis). In an on-going Phase 3 clinical trial, SVR were 96% (52/54) in patients with compensated cirrhosis treated with Technivie plus ribavirin for 12 weeks compared to 100% (49/49) in those treated for 16 weeks. In an on-going Phase 3 clinical trial conducted in Egypt, SVR rates were 97% (30/31) in patients with compensated cirrhosis treated for 12 weeks. Refer to ledipasvir/sofosbuvir CFU for use in this patient population
- **Genotype 4 patients who had previous virological failure with a direct-acting antiviral regimen:** Technivie regimen has not been studied and therefore, cannot be recommended. .
- **Populations unlikely to benefit from HCV treatment:** According to AASLD/IDSA HCV Guidelines, "patients with limited life expectancy for whom HCV therapy would not improve symptoms or prognosis do not require treatment. Chronic hepatitis C is associated with a wide range of comorbid conditions. Little evidence exists to support initiation of HCV treatment in patients with limited life expectancy (less than 12 months) due to non–liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized, and palliative care strategies should take precedence."
- **Chronic HCV-infected patients with minimal fibrosis** (METAVIR stage 0 or 1 based on an adequate liver biopsy specimen) and no other risk factors for liver disease are at lower risk for developing advanced liver disease in the short-term. After a thorough discussion of prognosis and treatment options, the provider and patient may agree to observation and defer treatment. Treatment should be reconsidered if liver disease progresses. Modifiable risk factors for progression of liver disease, such as alcohol use, should be addressed.

Use in Specific Populations (refer to Prescribing Information for comprehensive list of use in specific populations):

- **HIV**: **Co-infected patients should be managed in consultation with an experienced HIV treatment provider. Due to potential drug interactions with antiretrovirals and co-formulation with ritonavir, alternative treatment with ledipasvir/sofosbuvir is recommended in patients not receiving antiretroviral therapy OR where antiretroviral drug-interactions preclude the use of Viekira or Technivie (refer to ledipasvir/sofosbuvir CFU).** Ritonavir is also an HIV-1 protease inhibitor and can select for HIV protease inhibitor resistance-associated substitutions; the HIV status of all patients receiving this regimen should be known prior to the initiation of therapy to avoid inadvertently giving ritonavir-monotherapy to an unrecognized HIV infected patient. According to prescribing information, any HCV/HIV co-infected patients treated with Viekira or Technivie regimen should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance. However, potential antiretroviral regimens that can be co-administered with the Viekira or Technivie regimen need to be carefully evaluated prior to initiation of the HCV regimen. Refer to http://www.hep-druginteractions.org for potential options.
- **Decompensated cirrhosis:** Viekira and Technivie are **contraindicated** in patients with decompensated cirrhosis. Alternative treatment with ledipasvir/sofosbuvir plus ribavirin in patients with Genotype 1 and 4 is recommended (refer to ledipasvir/sofosbuvir CFU).
- **Hepatic Decompensation and Hepatic Failure in Patients with Cirrhosis:** Hepatic decompensation and hepatic failure, including liver transplantation or fatal outcomes, have been reported postmarketing in patients treated with Viekira or Technivie regimen. Most patients with these severe outcomes had evidence of advanced cirrhosis prior to initiating therapy. Reported cases typically occurred within one to four weeks of initiating therapy and were characterized by the acute onset of rising direct serum bilirubin levels without ALT elevations in association with clinical signs and symptoms of hepatic decompensation. These regimens are contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh B and C).
- **Hepatocellular carcinoma (HCC) or other cancer:** It is reasonable to treat HCV in any patient with HCC or other malignancy *if there is a high likelihood that the cancer has been cured*. Curative treatments for solitary or early stage HCCs within Milan criteria include resection and thermal ablation as well as liver transplantation (TACE, radioembolization, radiation therapy and targeted/chemotherapy are NOT considered curative). For those receiving resection or thermal ablation, if staging studies indicate good likelihood of success (absence of macrovascular invasion, clear margins, etc.) and if follow-up restaging studies show no evidence of cancer recurrence, then treatment of HCV may be offered.
- **Dosage adjustment hepatic impairment:**
    - For Viekira, no dosage adjustment in patients with mild hepatic impairment (Child-Pugh A); contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh B and C).
    - For Technivie, not FDA approved in patients with mild hepatic impairment (Child-Pugh A); contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh B and C).
- **Pre-Liver transplant (also see decompensated cirrhosis and HCC bullet above): <u>The decision to treat *any* patient awaiting transplantation should be made in consultation with the transplant center where the patient is listed and determined on a case by case basis</u>**. Close collaboration with the patient's transplant center is necessary to determine the timing of treatment initiation (pre- or post-) or whether treatment is appropriate given patient's prognosis.
- **Post-Liver Transplant:**
    - Viekira – although approved by the FDA for use in patients who have received a liver transplant, limited efficacy and safety data are available in this population. The ombitasvir, paritaprevir/ritonavir plus dasabuvir regimen + ribavirin for 24 weeks was evaluated in 34 post-liver transplant patients with HCV genotype 1 infection and fibrosis stages F0 through F2. SVR was achieved in 97.1% (33/34) with 1 patient relapse. Most patients received ribavirin doses of 600mg or 800mg/day; all patients with ribavirin dose reductions achieved SVR. In this study, tacrolimus was administered at a dose of 0.5mg every week or 0.2mg every three days; cyclosporine was administered as one-fifth of the daily pre-treatment dose; prednisone was dosed at <5mg/day. Based upon these data, the prescribing information states the recommended duration of

ombitasvir, paritaprevir/ritonavir plus dasabuvir with ribavirin is 24 weeks for liver transplant recipients infected with HCV genotype 1 with normal hepatic function and mild fibrosis (Metavir fibrosis score 2 or lower). Dosage adjustment of calcineurin inhibitors is needed. **Due to significant interactions with ritonavir, alternative treatment with ledipasvir/sofosbuvir plus ribavirin in patients with Genotype 1 is recommended to minimize potential for interactions (refer to ledipasvir/sofosbuvir CFU).**

- Technivie - not FDA approved for use in patients who have received a liver transplant (because solid organ receipts were excluded for Pearl-1clinical trial). In addition, due to significant interactions with ritonavir, refer to ledipasvir/sofosbuvir CFU for use in this patient population.

- **Renal Impairment:** No dosage adjustment of the Viekira or Technivie regimen is required in patients with mild, moderate or severe renal impairment. Regimens have not been studied in patients on dialysis. However, ribavirin is known to be substantially excreted by the kidney, and the risks of adverse reactions are greater in patients with impaired renal function. The total daily dose of ribavirin should be reduced for patients with creatinine clearance less than or equal to 50 mL/min as follows: creatinine clearance between 30-50ml/min use alternating doses of 200mg and 400mg every other day; for creatinine clearance <30ml/min or for hemodialysis use 200mg daily.
- **Substance or Alcohol Use:** All patients should be evaluated for current alcohol and other substance use, with validated screening instruments. Patients with active substance or alcohol use disorders may be considered for therapy on a case-by-case basis, and care should be coordinated with substance use treatment specialists as needed. **Thus, automatic disqualification of patients as treatment candidates based on a specific length of abstinence is unwarranted and is strongly discouraged**.
- **Mental Health Conditions:** HCV-infected patients with severe mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, posttraumatic stress disorder), as documented by psychiatric evaluation, who are engaged in mental health treatment should be considered for therapy on a case-by-case basis. The use of interferon-containing regimens is associated with worsening of these conditions. Patients should be managed in collaboration with Mental Health providers to determine the risks versus benefits of treatment and potential treatment options.
- **Hepatitis B:** No safety and efficacy data are available in this population; prescribing information for both Viekira and Technivie states that no dosage adjustments are needed in patients receiving tenofovir. No pharmacokinetic data are available for entecavir or lamivudine when co-administered with the Viekira or Technivie regimen.

Drug-interactions (Refer to full prescribing information for details):

- Ombitasvir, paritaprevir, and dasabuvir are inhibitors of UGT1A1, and ritonavir is an inhibitor of CYP3A4. Paritaprevir is an inhibitor of OATP1B1 and OATP1B3 and paritaprevir, ritonavir and dasabuvir are inhibitors of BCRP. Co-administration with drugs that are substrates of CYP3A, UGT1A1, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs.
- Paritaprevir and ritonavir are primarily metabolized by CYP3A enzymes and co-administration with strong CYP3A inhibitors may increase concentrations of paritaprevir and ritonavir. Dasabuvir is primarily metabolized by CYP2C8 enzymes and co-administration with CYP2C8 inhibitors may increase concentrations of dasabuvir. Ombitasvir is primarily metabolized via amide hydrolysis while CYP enzymes play a minor role in its metabolism. Ombitasvir, paritaprevir, dasabuvir and ritonavir are substrates of P-gp. Ombitasvir, paritaprevir and dasabuvir are substrates of BCRP. Paritaprevir is a substrate of OATP1B1 and OATP1B3. Inhibition of P-gp, BCRP, OATP1B1 or OATP1B3 may increase the plasma concentrations of the various components of HCV regimen.

Education and Screening:

- Counsel patient on general liver health, especially abstaining from alcohol use and limiting acetaminophen use to no more than 2g/day.
- Assess if patient previously screened and/or vaccinated for Hepatitis A and Hepatitis B vaccines; consideration vaccination if appropriate.
- Assess if patient previously screened for HIV; if not, consider testing for HIV.

Additional Resources:

- Refer to VA Office of Public Health Intranet Site http://vaww.hepatitis.va.gov

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